Host Susceptibility Initiative (HSI)

The National Toxicology Program (NTP) is launching a new initiative to study the genetic basis for differences in susceptibility that may lead to a better understanding of how substances in our environment may be hazardous to some individuals and not to others. Asthma, cardiovascular disease, cancer, diabetes, obesity, etc. are a few examples of diseases associated with multiple interacting genes of high, intermediate, or low penetrance that are induced or influenced by environmental exposure to toxins. The Host Susceptibility Initiative (HSI) will provide the NTP with a mechanism for planning, conducting, and analyzing multi-strain animal model assessment of the acute chemical toxicity, potentially associated with a human disease (see above list) or disease process (e.g., DNA damage, xenobiotic metabolism, hormonal signaling, mitochondrial energetics, etc.), as a result of genes and environment interactions. The NTP's current research and testing program evaluates acute to long term exposure to substances in isogenic strains of F344 rats and/or B6C3F1 mice to determine potential hazard. Through the HSI, the NTP scientists will take chemicals identified as toxicants in the research and testing program and evaluate them in multiple genetically diverse isogenic mouse strains to determine which strains are particularly sensitive or insensitive to the chemicals causing toxicity and associated disease. Significant genetic variation and disease susceptibility have been demonstrated in these isogenic mouse and rat strains.

The HSI will identify critical areas of research, perform initial toxicity and phenotyping studies, and thus provide data and biological samples for further investigation through the extramural and/or intramural research programs. These studies would complement the phenotyping studies and aim to identify the specific genes that confer sensitivity or resistance to toxicity and disease. Ultimately, the NTP expects to learn more about the key genes and pathways involved in the toxic response and the etiology of disease mediated by substances in our environment. Such an understanding of genes and environment interactions will lead to more specific and targeted research and testing strategies for the NTP scientists to use for predicting the potential toxicity of substances in our environment and their presumptive risk to humans and disease susceptibility. Additional tools and strategies may include the use of chemical libraries and high throughput toxicity analysis to identify toxins and their chemical features causing toxicity as well as the increased use of alternate comparative models, e.g., zebra fish, *C. elegans*, in NTP studies in order to understand the biological and genetic basis for development of environmentally responsive genes, their genetic diversity, and disease susceptibility. The HSI, thus, supports the NIEHS Genes and Environment Initiative.

There are many research strategies and genetic tools for identification of multiple genetic loci (quantitative trait loci) and determination of the high- to low-penetrant genes that control complex phenotypic traits, e.g., toxicity, immunotoxicity, cancer, neurotoxicity, or other disease responses. Based upon a number of meetings with extramural and intramural experts in the analysis of complex traits in mouse models and members of the NIEHS/NTP staff, a consensus was developed that an important primary tool to be used for identification of genes associated with specific phenotypes was haplotype association analysis using multiple inbred (isogenic) laboratory or inbred wildtype derived strains (diverse haplotypes) for correlation with phenotypes of interest. The completion of the dense genotyping (resequencing) of 15 isogenic mouse strains by

Perlegen-NIEHS provides a critical database and makes this approach feasible. If additional isogenic strains are required, limited genotyping may be carried out to infer haplotypes and perform the necessary phenotyping and association studies to provide critical data to the extramural and intramural scientists expert in those gene and environment interactions for additional research for determination of the genetic and environmental basis for the etiology of the disease as described.